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Letter to the editor

# Rehabilitation essential in the recovery of multifactorial subacute combined degeneration

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## 1. Introduction

Subacute combined degeneration (SCD) is a rapidly progressive myelopathy with a constellation of neurologic deficits, including progressive sensory abnormalities in the vibratory and proprioceptive domains, ascending paresthesias, gait ataxia, hyper- or hypo-reflexia, and, less commonly, motor weakness and loss of bowel and bladder control [1,2]. SCD is a result of dorsal and lateral spinal cord demyelination [3]. This form of myelopathy is secondary to a cobalamin or vitamin B12 deficiency, dietary insufficiency, malabsorption and/or, less commonly, excretion. Pernicious anemia, also known as autoimmune gastritis, is a common cause of vitamin B12 deficiency. Nitrous oxide ($N_2O$) exposure during recreational use or surgical intervention has also been reported to convert B12 to B12 analogues, which are then excreted in the urine, reducing B12 levels [3,4].

Up until now, much of the literature has presented the clinical manifestations of SCD primarily in the context of nitrous oxide ($N_2O$) abuse and exposure. Conversely, we report on a patient with a triple-insult SCD of the spinal cord, one insult secondary to non-compliance with B12 replacement therapy for pernicious anemia, one insult secondary to alcohol abuse, and one insult secondary to prolonged recreational use of nitrous oxide.

## 2. Case report

A 38-year-old man was triaged at a tertiary care setting for detoxification and alcohol withdrawal. He presented acutely with tremors, diaphoresis, insomnia, ataxia (progressive over the last three months), lower extremity paresthesias, decreased somatosensory perception, visual and auditory hallucinations, paranoia, and cognitive impairments. On questioning, he described copious alcohol consumption and nearly half a decade of $N_2O$ abuse with a recent escalation. His medical history included pernicious anemia, for which he was intermittently compliant with B12 injections, generalized anxiety disorder, major depressive disorder, and social phobia. He was compliant with his psychiatric medications, but not with his psychotherapy, and had a suicide attempt two decades prior.

Neurological findings were significant for decreased vibratory perception in his feet bilaterally; decreased pinprick and temperature perception below his ankles bilaterally; dysmetria on finger-to-nose testing; impaired tandem walking; low clearance, wide-based gait; patellae hyper-reflexia; bilateral Babinski sign; and a positive Romberg test. His mental status examination revealed an illogical thought process, slow, halting speech, depression, anxiety, paranoia and delusions consistent with an acute, substance-induced psychotic disorder. Lab results revealed a macrocytic anemia (hemoglobin 11.2 g/dL), low B12 (193 pg/mL), elevated methylmalonic acid (324 nmol/L), hyperhomocysteinemia (213 μmol/L), and a mild transaminitis. His intrinsic factor blocking antibody test confirmed his pernicious anemia. The chest X-ray and a non-contrast CT of the patient's brain were negative for acute processes. The patient was diagnosed with SCD.

Treatment included Librium, intramuscular B12 replacement therapy, Risperidone, and resumption of his prior psychiatric medication regimen. Five days into his hospitalization, he remained a fall risk, continued to display dysmetria on the finger-to-nose test, and still complained of visual hallucinations. However, he was more articulate, reported decreased sleep disturbances, and was stable for admission to acute inpatient rehabilitation.

Upon admission to the inpatient rehabilitation unit, evaluation his physical examination revealed a medium fall risk with a Berg balance score of 23/56, poor dynamic standing balance, and fair dynamic sitting balance. Contact guard assistance with straight cane was required for both bed mobility and transfers, ambulation, and stairway negotiation. For activities of daily living (ADL), he required supervision for bathing, toileting, toilet transfers, and dressing upper extremities; minimum assistance for bath transfers; and moderate assistance for dressing lower extremities. In terms of cognitive status, impairments included deficits in delayed recall, visuospatial and executive functions.

The patient underwent a three week acute inpatient rehabilitation course with intensive therapy consisting of two hours of physical therapy and one hour of occupational therapy each day five days per week. Physical therapy was used to retrain gait, ambulation, transfers, bed mobility and use of an assistive device and occupational therapy was used to retrain in ADLs, community reintegration, and cognitive training. The rehabilitation therapy helped the patient regained full sensory perception of his lower

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extremities and made impressive gains in ADLs, including independence during bathing, toileting, toilet transfers, bath transfers, bed mobility, dressing of upper/lower extremities and ambulation on even surfaces. We noted improvements in other areas of the assessment, however, his recovery was not complete. The patient was still a low fall risk status with a Berg balance of 45/56, showed impairments on dynamic balance testing, single leg activities, and ambulation on uneven surfaces and negotiation of ramps and stairs. Although his cognition appeared intact and thought process became more logical, his thought content was still impaired and contained thought insertions while his mood was frustrated, anxious, depressed and blunted. He was subsequently discharged to an inpatient substance abuse program.

## 3. Discussion

This is a unique case of SCD and acute psychosis secondary to a triad of insults in a young patient. Pernicious anemia, chronic alcoholism, and nitrous oxide abuse resulted in low B12 levels, poor intestinal absorption of B12, and excretion of B12 analogues, respectively. These factors prompted an early myelopathic onset despite the fact that SCD classically occurs after the age of 60 [2,4,5]. With intensive rehabilitation, we witnessed a complete resolution of sensory deficits and numerous improvements in function. However, some lingering deficits in balance and thought content compel us to suggest further research guidelines to increase our understanding and improve our treatment of the myelopathy.

Given its increased use today, $N_2O$ abuse and exposure should be screened for in patients with a progressive myelopathy. Factors that are positively correlated with complete resolution include a younger age, male gender, early medical intervention, less severe neurologic deficits, and less spinal cord involvement. Older age, sensory deficits, anemia, positive Romberg and Babinski signs are negatively correlated with complete resolution. Approximately 14% of SCD patients experience complete resolution and 86% experience improvement with residual deficits with B12 therapy [1]. Considering his multiple negative correlates, including a longer duration of illness, pernicious anemia, sensory deficits, positive Babinski sign and positive Romberg, a complete resolution was not expected in our patient. Direct observance of B12 administration and cessation of substance abuse halted the progression of neurological damage while intensive rehabilitation therapy led to significant functional improvement. As demonstrated in this case, rehabilitation can be used to assess progress, improve recovery, and increase functionality in SCD and should be considered an essential aspect of medical intervention.

Despite significant improvements in patients who undergo medical intervention, we have yet to achieve complete resolution of neurological deficits in SCD. The limited understanding of the role that B12 deficiency plays in the pathogenesis of SCD may contribute to this. Thus far, B12 deficiency is known to cause myelin sheath swelling and vacuolation in SCD. The latest hypothesis developed from studies on the gastrectomized rat model of human SCD suggests that B12 deficiency disrupts the normal balance of cytokines and growth factors that then contributes to the pathogenesis of SCD. More specifically, B12 deficiency up-regulates spinal cord synthesis and cerebral spinal fluid (CSF) levels of myelinotoxic cytokines involved in systemic inflammation such as tumor necrosis factor-alpha (TNF-$\alpha$) and soluble cluster of differentiation 40 ligand dyad (sCD40L), and a myelinotoxin, nerve growth factor (NGF). Moreover, B12 deficiency down-regulates the anti-inflammatory cytokine interleukin-six (IL-6), and the myelinotrophic growth factor, epidermal growth factor (EGF) [4].

Studies confirm that elevated levels of TNF-$\alpha$ and reduced levels EGF are found in the serum and CSF in patients with SCD. B12 replacement therapy corrects CNS cytokine and growth factor abnormalities and results in the reappearance of normal myelin [4,6]. In animal models, treatment with either IL-6, EGF, anti-TNF-$\alpha$, anti-CD40L or anti-NGF antibodies prevents the onset of myelinolytic lesions [6].

Although the hypothesis has potential implications for the future treatment of SCD, its limitations should be considered since most of its supporting data stem from animal studies. Studies need to be undertaken with patients to confirm changes in IL-6, sCD40L, and NGF levels. Further studies should test if treatment with TNF-$\alpha$ antibody (anti-TNT-$\alpha$), CD40L antibody (anti-CD40L), IL-6 and EGF can prevent myelinolytic lesions in humans as they have in animals and used as part of a treatment regimen that increases the likelihood of complete resolution in patients with lesions secondary to severe SCD. Further research is needed to define precisely how changes in levels of cytokines and growth factors precipitate SCD. Despite these limitations, the initial human data provide evidence that a spinal tap for changes in cytokine and growth factor levels can be used as part of a thorough diagnostic work up.

Another unique feature of this case was the concurrent diagnosis of an acute, substance-induced psychotic disorder. A dearth of literature exists on acute psychosis in the context of both $N_2O$ exposure or abuse and B12 deficiency. Patients with $N_2O$ exposure or usage and B12 deficiency both present with similar symptoms of memory loss, psychosis, hallucinations [7,8]. The combination of the acute on chronic B12 deficiency and the $N_2O$ abuse of our patient led to a compounded clinical picture including severe hallucinations and paranoia, requiring medication and psychiatric monitoring and treatment during his hospitalization.

## 4. Conclusion

In conclusion, physicians should be cognizant of the symptoms and pathogenesis of SCD. Recreational abuse of $N_2O$ has been increasing, therefore, $N_2O$ induced SCD and/or psychosis should be considered in a differential diagnosis when a patient presents with a progressive myelopathy and/or mental status changes. Physicians should screen for $N_2O$ abuse or exposure and request laboratory tests of serum B12 levels, homocysteine, methylmalonic acid and, if a spinal tap is warranted, CSF levels of TNF-$\alpha$ and EGF. Also, further studies are needed to validate the current growth factor and cytokine imbalance hypothesis in humans and to test if anti-TNF-$\alpha$, anti-CD40L, IL-6 and EGF can be used as part of the medical intervention. Most importantly, early B12 replacement and rehabilitation tailored towards the patient's functional and neuropsychiatric rehabilitation can minimize the extent of the neurological damage. As we have learned in this case, intensive rehabilitation can facilitate recovery even in the most dire of circumstances. Our patient, who delayed the presentation of his multifactorial SCD, was able to regain complete sensation in his lower extremities and even independence during ADLs.

## Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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